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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,660	11/28/2005	Gunther Harth	51326-00005 NAT	6518

45200 7590 08/04/2006

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EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,660	HARTH ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

The instant application is a 371 of PCT/US03/36705 which claims benefit of provisional applications 60/426,502 filed 11/15/2002, and 60/430,407 filed 12/02/2002. Claims 1-14 are currently pending and are examined on the merits herein.

Claim Objections

Claims 3-4, 10 and 11-13 are objected to because of the following informalities:

Claim 3 use the abbreviation α-Me-MSO for the chemical name, alpha-methyl-**D,L**-methionine-**SR**-sulfoxamine. Claims 4 and 10 use the same abbreviation, α-Me-MSO, for the chemical name, alpha-methyl-**L**-methionine-**S**-sulfoxamine. Claim 3 also uses the abbreviation α-Et-MSO for the chemical name alpha-ethyl-**D,L**-methionine-**SR**-sulfoxamine, while claims 4 and 10 use the same abbreviation for alpha-ethyl-**L**-methionine-**S**-sulfoxamine. Claims 11-13 depend from both claims 3 and 4. Furthermore, throughout the specification the two abbreviations are used. It is not clear which specific compound the abbreviation refers to.

Appropriate correction is required.

Claim 3 is objected to because of the following informalities: The recitation of the names alpha-methyl-**D,L**-methionine-**SR**-sulfoxamine and alpha-ethyl-**D,L**-methionine-**SR**-sulfoxamine does not adequately point out the stereochemistry of the compositions. A racemic mixture on the other hand does not require a designation of the stereochemistry. With the D,L and SR designations one of ordinary skilled in the art will not know the claimed compound's stereochemistry. Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-14 of copending Application No. 10/715,679. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,013,660 in view of Griffith OW et.al (U: PTO-892, Cited by the examiner).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of for treating mammalian disease conditions associated with infection of pathogenic mycobacterium comprising the steps of administering L-methionine-S-sulfoxmine (MS) to a mammal in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal. The '660 patent further claims the use of said compound for the treatment of several mycobacterium bacteria including, M.tuberculosis, and M.avium. The '660 patent further attributes the activity of MS and its analogs to their ability to inhibit the activity of the extracellular enzyme glutamine synthetase (GS) an extracellular protein which is essential for the growth of M.

tuberculosis and other closely related pathogenic intracellular mycobacteria. Inhibition of the activity of M. tuberculosis glutamine synthetase, specifically that enzyme which is released extracellularly was found to inhibit the growth of M. tuberculosis cells resulting in the inhibition of bacterial growth. (Column 5, lines 50-61).

The claims of the instant application is drawn to compositions including alpha-alkylated methionine sulfoximines and methods of treating pathogenic mycobacterial infections using said compounds.

The '660 patent does not expressly disclose alpha alkylated L-methionine-S-sulfoximine or a racemic mixture of the same or other alpha alkylated butyrates for the treatment of pathogenic mycobacterium infection.

Griffith et. al. discloses the use of alpha-alkylated analogs of methionine sulfoximine, in particular alpha-ethyl-methionine sulfoximine for the selective inhibition of glutamine synthetase. (Page 2333, Abstract). Methionine sulfoximine is a known convulsant. (Page 2333, Column 1, Paragraph 2, lines 1-5). Griffith et. al. discloses that while methionine sulfoximine induces convulsions at a dosage of 1mmol/kg, alkylated methionine sulfoximines, in particular alpha-ethyl-methionine sulfoximines only produced convulsions at a much higher dosage. (Page 2335, Column 2, Paragraph 4, and Page 2336, Column 2, Paragraph 1).

One of ordinary skill in the art at the time the invention was made would have been motivated to employ alpha-alkylated methionine sulfoximines to treat mycobacterial infections because alpha-alkylated methionine sulfoximines were well known for their selective inhibition of glutamine synthetase and the '660 patent shows

that the inhibition of glutamine synthetase by methionine sulfoximine leads to the inhibition of mycobacterial growth. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the disclosed compounds of Formula I, does not reasonably provide enablement for all gamma-substituted alpha-amino-alpha alkyl-butyrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

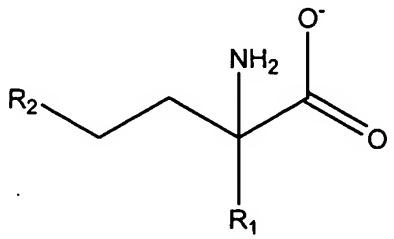
(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant application relates to the use of α-alkyl and γ-sulfur/phosphorous substituted butyrates for the treatment of mycobacterial infections.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims:

Claims 5-6 and 11-13 are very broad because it will read on any gamma-substituted alpha-amino-alpha alkyl-butyrate molecule. The general structure of gamma-substituted alpha-amino-alpha alkyl-butyrates is as follows;



The R1 substitutent here could be any alkyl group, while R2 could be any group without any limitation.

The state of the prior art: The prior art includes the use of many molecules of the general structure given above with tetrahedral sulfur and phosphorous substitutions in the gamma position for the treatment of bacterial infections. It is well established that α-alkyl analogs of methionine sulfoximines are potent inhibitors of glutamine synthetases. (PTO-892, Cited by the examiner; Griffith OW, et. al., The Journal of Biological Chemistry; 254(4), 1979, 1205-1210). Griffith et. al. discloses compounds that read on the above formula. (Page 2335, Column 1, Table 1). Phosphonic acid analogues of

glutamic acid and alpha-alkylated glutamic acid are also well known for their antibiotic activity. (PTO-892; Cited by the examiner; Lejczak B; et.al., Experimentia 37, 1981, 461-462). Leijcazk et. al. discloses phosphonic acid derivates that read on the above formula. (Page 461, Column 2, Table, Compounds 3 and 4). Furthermore, L-methionine-S-sulfoximine is known to selectively inhibit pathogenic Mycobacterium tuberculosis. (PTO-892, Cited by the examiner; Harth et. al. J.Exp. Med. 189(9), 1425-1435, 1999). The only difference between the compounds of the instant application and the compound disclosed to have anti-microbacterial activity in Harth et. al. is the presence of a methyl group instead of a H at the R1 position.

The predictability or unpredictability of the art: The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses many, different, divergent functional substitutions at the α and γ positions giving various compounds with divergent and highly unpredictable properties. For example, the phosphonic acid compounds disclosed in Leijcazk (discussed above) and the sulfoximine compounds disclosed in

Griffith et. al. (discussed above) all read on compounds of claim 5, but they have different structures.

The amount of direction or guidance presented:

The specification discloses the use of tetrahedral sulfur and phosphorous substituted butyrates (Page 5, Paragraph 13 and Figure 6), as well as alpha substitutions involving 2-8 carbons (Page 5, Paragraph 14 and 15). However, no other gamma substitutions involving any other functional groups is disclosed in the specification.

The presence or absence of working examples:

Examples 1-8 discloses compounds with tetrahedral sulfur and phosphorous substitutions in the gamma position. However, there are no other functional groups disclosed. Thus, examples 1-8 are not considered to represent each and every compound encompassed by the claims here.

The lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

The quantity of experimentation necessary:

In order to determine which of the varying functions groups in the gamma and alpha positions of the claimed compounds, one of ordinary skill in the art will have to perform substantial experimentation. Experimentation will include the synthesis of compound with many different functional groups in the gamma and alpha positions and

identifying varying functional groups for activity against glutamine synthetase. Such experimentation will involve the commitment of highly skilled organic chemists, microbiologists, biochemists and those with expertise in combinatorial chemistry. As such, undue experimentation is necessary to practice the invention to its full scope.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicant fail to provide information sufficient to practice the claimed invention for the prevention of diseases claimed herein absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of the phrase "wherein said anti-mycobacterial composition effectively inhibits MbGS but does not substantially inhibit

mammalian glutamine synthetase (MGS) in vivo" renders the claim indefinite. The dosage range to achieve such differential effect is not clear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffith et. al. (X: PTO-892; Cited by the examiner: The Journal of Biological Chemistry, 253(7), 1978, 2333-2338) or Griffith et. al. (U: PTO-892; Methods in Enzymology, 143, 1987, 286-291; Ctied by the examiner).

Griffith et. al. discloses that compositions containing α-methyl-DL-methionine-(S or R)-sulfoximine and α-ethyl-(D or L)-methionine-(S or R)-sulfoximine are useful for the inhibition of glutamine synthetase. (Page 2336, Table 2 and Abstract). Note that a racemic mixture will have each enantiomer present in the mixture, and the single enantiomer of claim 4 will be present in a racemic composition.

The recitation "anti-mycobacterial composition" is considered the intended use of the claimed composition. Note that it is well settled that "intended use" of a composition or product, e.g., "anti-mycobacterial composition", will not further limit claims drawn to a composition or product, so long as the prior art discloses the same composition

comprising the same ingredients as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364,1368 (Fed. Cir. 2004). *See* MPEP 2110.4.

Note that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

In case of the present application, the property of the composition comprising the claimed compounds in inhibiting mycobacterial glutamate synthetase without

substantially inhibiting mammalian glutamine synthetase in vivo is inherently present in the composition of Griffith et. al.

Claim 1 is further rejected under 35 U.S.C. 102(b) as being anticipated by Lejczak et. al. (PTO-892; Cited by the examiner).

Lejczak et. al discloses the synthesis and use of α-methylated-methionine-phosphonate as well as γ-methylated phosphinates as antimicrobial agents. (Page 461, Column 2, Table, Compounds 3 and 4).

Note the discussion above regarding the recitation "anti-microbial composition," and the recitation "mycobacterial composition effectively inhibits MbGS but does not substantially inhibit mammalian glutamine synthetase."

Also note, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

Lejczak et. al. discloses composition identical to those claimed herein. The preferential inhibitory property of compounds claimed herein is inherently present in the

identically disclosed compounds of Lejczak et. al. Thus, compounds of claim 1 are anticipated by Lejczak et. al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harth et.al. (PTO-892, Cited by the examiner; J.Exp. Med. 189(9), 1425-1435, 1999), in view of Griffith et.al. (X; PTO-892, Cited by the examiner; Methods in Enzymology, 143, 286-291).

Harth et. al. teaches that pathogenic Mycobacteria secrets large number of proteins in to extracellular milleu. One of the abundantly released proteins is the enzyme glutamine synthetase. However, nonpathogenic mycobacterial microorganisms do not release glutamine synthetase into the extracellular milleu. (Page 1425, Column 2, last paragraph and Page 1426, Column 1, first paragraph). Harth et. al. further teaches that the inhibition of enzyme glutamine synthetase blocks bacterial multiplication. (Page 1426, Column 1. Paragraph 3). Harth et. al. teaches that inhibition of extracellular glutamine synthetase blocks bacterial multiplication both in broth medium and in human mononuclear phagocytes and that growth inhibition is correlated

with a marked reduction in the amount of virulence-associated cell wall component poly-L-glutamate/glutamine. (Page 1426, Column 1. Paragraph 3). Harth et. al. notes that; "Specifically, our study demonstrates that treatment of *M. tuberculosis* with a drug that inactivates extracellular glutamine synthetase inhibits mycobacterial growth. Hence, drugs functionally analogous to L-methionine-S-sulfoximine, but perhaps with even greater specificity for *M. tuberculosis* enzyme relative to the mammalian enzyme have great potential as antibiotics against this pathogen." (Page 1434, Colunn 1, Pargraph 5, line 13 to Column 2, paragraph 1, lines 1-6). Harth et. al. further compared the sensitivity of glutamine synthetase inhibitors on purified *M. tuberculosis* glutamine synthetase to mammalian glutamine synthetase. (Page 1427, Column 1, Paragraph 2, lines 10-15). Harth et. al. further discloses the use of conventional antibiotics in combination with L-Methionine-S-Sulfoximine, in particular isoniazid. Harth et. al. notes that, "The most pronounced effect on bacterial growth was observed for isoniazid and rifampin at one-tenth their minimal inhibitory concentrations in combination with 0.2μM L-methionine-S-sulfoximine." The authors further notes that, "This result is consistent with the hypothesis that the inhibitory effect of L-methionine-S-sulfoximine on the extracellular glutamine synthase effects the integrity of the M-tuberculosis cell wall so as to allow antibiotics greater access to the bacterial cytoplasm." (Page 1433, Column 2, Paragraph 2, lines 1-23). Harth et. al. further teaches that, of the possible four racemic forms of the inhibitor (D, or L)-methionine-(S or R)-sulfoxamine, only L-methionine-S-sulfoximine is active against glutamine synthetase. (Page 1429, Column 1, Paragraph 2, lines 7-11).

Harth et. al. does not expressly disclose the use of the particular α-alkylated compounds of formula I with methyl or ethyl substitution at the R-1 position for inhibiting, treating or palliating mycobacterial infections; in particular Harth et. al. does not disclose the use of alpha-methyl-(D or L)-methionine-(S or R)- sulfoxamine or alpha-methyl-L-methionine-S-sulfoxamine or alpha-ethyl-(D or L)-methionine-(S or R) -sulfoxamine or alpha-ethyl-L –methionine-S-sulfoxamine as anti-mycobacterial agents.

Griffith OW teaches that α-ethylmethionine sulfoximine, one of the mycobacterial inhibitors of the present application as a selective inhibitor of glutamine synthetase. Griffith OW notes that, "Selective inhibition of either glutamine synthetase or γ-glutamylcysteine synthetase is possible in vitro or in vivo using analogs of methionine sulfoximine. Thus, α-ethylmethionine sulfoximine inhibits only glutamine synthetase whereas prothionine sulfoximine inhibits only glutamine synthetase whereas porthionine sulfoximine, butathionine sulfoximine and higher S-alkyl analogs of methionine sulfoximine are specific inhibitors of γ-glutamylcysteine synthetase." (Page 287, Paragraph 1, lines 9-17).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use α-ethylmethionine sulfoximine as an inhibitor of mycobacterial glutamine synthetetase because, Griffith teaches that α-ethylmethionine sulfoximine is a selective inhibitor of glutamine synthetase and Harth et. al. teaches that the growth of pathogenic mycobacteria can be inhibited by the inhibition of glutamine synthetase, in particular analogues of methionine sulfoximine.

One having ordinary skill in the art would have been motivated employ particular alpha-alkylated compounds herein, because, Harth et. al. suggests the use of analogues of methionine sulfoximine, and α-ethyl-methionine sulfoximine, the compound instantly claimed, is a well known analogue of methionine sulfoximine, known for its activity against glutamine synthetase. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions.

As noted in MPEP 2144, "If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id. Dillon, 919 F.2d at 697, 16 USPQ2d at 1904-05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that

would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Thus, the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson ME. (PTO-892, Cited by the examiner; Chemico-Biological Interactions, 111-112, 1998, 1-14), in view of Harth et. al. (PTO-892; Cited by the examiner).

Anderson ME teaches that methionine sulfoximine is shown to inhibit both glutamine synthetase and γ-glutamylcysteine synthetase and it leads to convusions. (Page 5 last paragraph to page 6, lines 1-10). The γ-glutamylcysteine synthetase enzyme is involved in the synthesis of glutathione. (Abstract, and Page 2, Figure 2). Administration of methionine sulfoximine to rodents leads to convulsions. (Page 6, lines 3-7). Anderson ME recommends the use of ascorbate to prevent oxidative damage due to glutathione deficiency. (Page 6, paragraph 2).

Anderson et. al. does not expressly disclose the use of chirally pure L-methionine-(S or R)-sulfoximine enantiomer.

As discussed above, Harth et. al. discloses that of the possible four racemic forms of the inhibitor (D or L)-methionine-(S or R)-sulfoxamine, only L-methionine-S-

sulfoximine is active against glutamine synthetase. (Page 1429, Column 1, Paragraph 2, lines 7-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer L-methionine-(S or R)-sulfoximine with ascorbic acid because ascorbic acid is well known to reduce convulsions associated with methionine sulfoximine and the L-methionine-S-sulfoximine enantiomer is known to be the active the agent against glutatmine synthetase.

One of ordinary skill in the art would have been motivated to co-administer ascorbic acid with L-methionine-(S or R)-sulfoximine because the combination is expected to produce beneficial therapeutic effects.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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